Medical treatment and medical quantitative measurement of vocal cord nodules, a prospective case-control study.

Patients compared with normal persons in Copenhagen and Zagreb

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ABSTRACT

Objectives
The aim of the study was to assess the possibility, that many benign voice disorders and vocal cord nodules could be improved by medical diagnosis and treatment of infections, allergies, reflux, environmental provocations of dust, noise, dry air and others, and basic medical voice hygiene advice. In addition, in order to investigate the effect of possible different aetiology and treatments across nations this study involved two very different centres for recruitment and treatment.

Methods of study
Adults with vocal cord nodules seen for the first time, in a period of two months, were measured prospectively 2 times with one month interval in a clinic in Zagreb (n=6) and Copenhagen (n=10), based on a common protocol, in this pilot study. No males were found in the period. The female patients were compared with females of the same ages with normal voices selected consecutively in the same period, (n=13 in Denmark and n=11 in Croatia).

The inclusion criteria consisted of video stroboscopy clips documenting nodules (primary outcome). A Voice Related Quality Of Life (V-RQOL) questionnaire, filled in by the patient, acoustical measurement of Jitter % and Shimmer % with the program MDVP and a GRBAS voice perception test (second outcome) were based on a common protocol, with evaluation before and after the medical treatment with one months’ interval.

The procedure was carried out two times for the controls without voice complaints as well, including evaluation of the vocal cord function with video stroboscopy, V-RQOL questionnaire, Jitter %, Shimmer % and a GRBAS voice evaluation test. Medical diagnosis and treatment included infections in the airways, allergies, reflux, environmental provocations and others. Medical voice hygiene instruction was given. The V-RQOL questionnaire was used to identify the patients’ complaints.
The multidimensional voice program was applied for the acoustical measurements of Jitter % and Shimmer % (Multi Dimensional Voice Program by Key-Elemetrics, MDVP) because it was also available in Zagreb. Theselection of the control samples of normal females was made, in the way that every time a female patient joined the study one or two age related females with normal voices, accepted to be evaluated with the same medical and voice measures before and after one month.

**Results and Conclusion**

Vocal cord nodules were reduced to small mucosal swellings in half of the Danish, but in none of the patients from Zagreb on the second videoclips of digitized video stroboscopies after one month. The V-RQOL questionnaire showed that the the social, psychological and the physical functioning domains became better but not normal in most of the clients (p<0.01). There was a generally worse physical functioning in the Danish samples than in the Zagreb samples both before and after treatment (t-test p<0.05). In the MDVP programme at the second examination the /i/ Shimmer % showed improvement after treatment as compared with the normal controls (t-test p<0.02), for the /a/ Shimmer %, the same tendency was seen (t-test p=0.053). No differences were found between the two centres.

The medical diagnoses and treatment, and the quantitative analysis of a voice related quality of life questionnaire, acoustical analysis of Shimmer % and Jitter % in the MDVP and the GRBAS voice perception test were shown to be useful in the two clinics in Copenhagen and Zagreb.

**Introduction**

Little research into the treatment of vocal cord nodules has been clinically evidence based. A
Cochrane evidence based Library review, found that no studies on the surgical versus non-surgical intervention for vocal cord nodules were prospective, blinded and randomised (1). Since the Cochrane review was published, the authors of the present study have been able to find two published prospective studies involving the treatment of vocal cord nodules none of which fulfil the criteria for such studies laid down in the Cochrane Handbook for evidence based studies. Benninger found no difference between laser and micro dissection with cold instruments on benign vocal cord disorders (2) unfortunately not comparing the results with spontaneous healing. McKenzie and al. published a prospective, randomised study showing no effect of logopedic voice therapy on hoarseness using frequency and intensity variation (Jitter and Shimmer) measures (3), the amount of patients in the groups being too small for evidence based statistical calculations. A voice related quality of life questionnaire (V-RQOL) was suggested by Hogikyan et al. (4) to assess the voice following type 1 thyroplasty for unilateral vocal fold paralysis. A purpose of the questionnaire was to identify social, psychological, physical functioning and overall voice related quality of life. The secondary calculations for weightening of the groupings in that study were not included in our analyses (4). A recent pilot study by the present first author et al. (5) has shown that after treatment of infections, allergies, reflux and environmental provocations of dust etc.the voice related quality of life improves. That study also found that the used medical voice hygiene instructions alone, such as advice by the ear-nose-throat specialist of correction of posture, the use of the diafragm muscle, intonation patterns and resonance, will result in an improvement shown by the V-RQOL questionnaire.

As shown in the above mentioned review (1) many retrospective studies have been published on the treatment of vocal nodules (1). Of interest in particular is that dysphonia, including vocal cord nodules, in the past was considered to be of functional origin, resulting from vocal abuse, misuse and/or overuse. The disorders were generally treated educationally and/or surgically. The new
aspects of treatment of infections, allergies, reflux etc. have been elucidated in the later years among others due to new measurement possibilities (6-17).

The aim of the study was to assess the possibility, that many benign voice disorders and vocal cord nodules could be improved by a medical diagnosis and treatment of allergies, infections, reflux, environmental disorders and others. In addition, because of possible differences in aetiology and treatments across nations, this study involved two very different centres for recruitment, objective voice pathology diagnosis and treatment.

**Methods of study**

In the protocol for this pilot study of medical treatment of vocal cord nodules for the test persons, the inclusion criterion was visually documented with stored digital clips of video stroboscopies of vocal nodules of adults over 18 years. Written consents were made traditionally. The inclusion period was two months. A control sample of individuals with normal voices was made, in the way that every time a patient joined the study one or two age related females with normal voices in the two clinics accepted to be evaluated with the same medical and voice measures before and after one month. In this way comparable controls of approximately the same ages without voice complaints were included. The procedure was the same at both centres in Denmark and Croatia. Standard exclusion criteria of chronic diseases and malignancy were used.

The degree of subjective complaints of dysphonia was evaluated by the voice related quality of life of the patients and controls using the Voice-Related Quality Of Life questionnaire (4). Objective measurement including frequency and intensity variation was made of jitter %, shimmer %, stored in the Multi Dimension Voice Program by Key-Elemetrics (14). All stored /a/, /i/ and test sentences were evaluated by 2 experienced phoniatricians and 1 speech therapists in Denmark and Croatia. The groups of patients and controls in Denmark and Croatia
were measured with one month’s interval before and after an updated general medical diagnosis and therapy as described beneath, and a standardised medical voice hygiene advice (5). It was noted that some of the patients and controls had more than one medical diagnosis of allergy, infections, reflux, environmental provocation etc.

The primary outcome was reduced vocal cord nodules as documented by digitised clips of video stroboscopies describing the vocal cords. Secondary outcomes were V-RQOL questionnaires, jitter and shimmer % measured with MDVP (14) and the GRBAS voice perception test as described and evaluated in the literature (15).

The updated medical diagnosis and intervention for the laryngeal mucosa included routine examination of local infection, diagnosed with microbiological swabs of virus PCR and upper airways bacteria and treatment in concordance with routine microbiological advice from The Serum Institute of Denmark and the Ear- Nose- Throat dpt. in Zagreb.

The diagnosis of inhalation allergy of pollen, animal hair and dust was made as a screening IGE standard bloodtest by the Copenhagen Central Laboratory and the University of Zagreb.

A screening test for IGE mediated food allergy of milk, wheat, fish, nut, soya and peanut was also made as a routine. Careful treatment of allergies was made when present with medication, local and universal with antihistamins and cortison derivates when needed, exclusion of known provocation, change of diet and others. Non-IGE mediated allergies were also diagnosed by scientific updated systematic exclusion and provocation, and relevant diet change was made.

Acid-, air- and enzyme- reflux (Gastro-Esophageal Reflux Disease or Laryngo- Pharyngo-Reflux Disease), and helicobacter infection was looked for routinely and when diagnosed by stroboscopy and gastroscopy dependent on the patients’ symptoms, acid- or acid- pump inhibitors and eventual relevant antibiotics were given, combined with diet advice and change of life style (5).

Environmental provocations such as an indoor climate of noise, dryness and dust and other
provocations and disorders (e.g. hormonal disease) were looked for, diagnosed and treated.

Medical therapy was also applying to voice hygiene advice: of the voice source of the glottis related to posture, abdominal respiration including awareness of the function of the diafragm muscle, intonation pattern as regulated only from the brain and stability of resonance including relaxation of the jaw as suggested by Froeschels and others (18,19,20).

Details of measurements:

The GRBAS perception analyses included the stored vowels /a/, /i/ and one sentence of vowels in MDVP. In Danish and Croatian (the blue spot is on the key again - den blå klat er på nøglen igen (Danish) – plava je mrlja opet i na kljucu (Croatian)) text were used.

The perceptual variables on a visual scale from 1-100 were overall severity, roughness, breathiness, strain, and also deviant loudness and pitch.

The stored vowels and sentences in the MDVP were analysed in the Excel program for statistics. The analysis of peak to peak jitter % and shimmer % were used for statistics (jitter at 1.measurement and shimmer at 1.measurement versus jitter at 2. measurement and shimmer at 2. measurement) (21).

The subjective voice complaints of the patients in the V-RQOL test questionaires, were filled in by the patients alone before and after one month of medical treatment and medical hygiene voice advice.

In order to describe the results in this pilot study t-tests were used. The difference in jitter% and shimmer% from 1. to 2. examination was analysed by a 2-way F-test analysis of variance grouped by centre and treatment.

Results
Table 1
The groups of patients with nodules and controls are presented in table 1. A disease of the voice in the past was found in 3 patients in Denmark and 4 in Croatia. Of interest is that in this case-control study, in the patient group with voice nodules it was more likely that they had an upper airway infection than in the group without voice problems. This is unlike the rest of the disorders complaints. The swap-documented virus and bacterial infection of the upper airways was found in 5 and 4 cases in Copenhagen and Zagreb respectively.
Symptomatic IGE mediated allergy of the upper airways was found in 4 patients in Denmark.
Reflux (Gastro Esophageal Reflux Disorder or Laryngo Pharyngeal Reflux Disorder) and abnormal antibody to helicobakter pylori was found in 3 patients in Denmark and in 2 patients in Croatia respectively.
In the control group with good voices 9 had IGE mediated allergy and 3 reflux (GERD or LPRD) and one was found with abnormal helicobakter pylori (IGG) antibodies in the Danish group but none in the Croatian group.
This study represents a small population, but the vocal cord nodules could possibly be explained by the medical disorders comparing test persons with controls. However it is taken into account that some of the patients had several disorders and no test has been carried out on these data. A clinical larger amount of patients is suggested to document the results.

Table 2
The results of the V-RQOL questionnaire of subjective voice complaints (see Appendix A) are presented in Table 2. It may be noticed that all controls score 1 on all items on both occasions. When comparing the scores of each patient before and after the treatment the general tendency, with very few exceptions, is that the score value has been reduced indicating an improvement. The
number of 1-scores, indicating no problem, has increased for most patients after the treatment. The use of traditional statistical calculations by a t-test based on the mean score values shows lower mean score values after treatment for the V-RQOL questionnaire both in Copenhagen and in Zagreb ($p < 0.01$), the score of the physically voice functioning domain was found to be lower only in Copenhagen ($p < 0.05$).

As the score values are only indicating an ordering of the degrees of complaint not exact measured values, these values form together only an ordinal scale. The difference between two consecutive values cannot be considered to be constant, as is the case for a linear scale, which is assumed by the use of the t-test. The t-test has been used here in accordance with the traditions in the field. The test results shall be considered as informative.

Table 3

Table 3 shows scored test values for the GRBAS voice perception test for patients with vocal nodules and for controls with good voices. Two values have been scored on each item for each individual, with one month’s interval, before and after a medical treatment and medical voice hygiene advice. A relation to the medical sub-grouping of diagnoses was not found in this material (e.g. allergy vs. infection vs. reflux).

In GRBAS voice perception test a score under 33 indicates a good voice function (15). An inspection of the tables shows that, with two exceptions, all controls score 1 on all items on both occasions, and the two exceptions were both well below 33. With regard to the patients, one Croatian had good scores on all items before the treatment, among the other patients all had one or more score values beyond the range before treatment. After treatment one or more score values were reduced for all patients except for three, two Danish patients, both with high score values, and
one Croatian, whose score values were close to the good range. For the 8 Danish patients, whose scores had been reduced, all scores recorded after treatment were within the good range (below 33) except for the strain scores of two patients. For the 5 Croatian patients with scores above the good range, the reduction in score values after the treatment was smaller than for the Danes, and only a single score value for one Croatian patient was reduced to the good range.

A traditional t-test based on averages of score values showed a significant reduction for all patients both for Danish and Croat patients. Also in this case the result of the t-test should be considered as only informative and indicative, as also in this case the score values do not form a linear scale as a difference of 10 units between two score values does not correspond to the same clinical difference for small and for large values.

Table 4

In table 4 results are presented of the stored average jitter% and shimmer % (of intonated 3,7 to 4,0 sec.) /a/ and /i/ in the patients speaking area, measured with the multidimensional voice program (MDVP). Tests for the measurements before and after medical treatment of patients with vocal nodules in Zagreb and Copenhagen of the first and second examination of jitter % show no statistical differences.

For /i/ shimmer% there was a difference between patients and controls. The measurements from the first to the second examination for /i/ shimmer % showed reduced values, presenting possible treatment effect (p<0.02). For /a/ shimmer % the same tendency was seen (p=0.053). There was a common difference for the two centres.

An experimental measure at the first visit of sentence jitter (% or/= irregularity) (the blue spot is on the key again) showed that the mean sentence jitter irregularity in pathological voices was
different from normals in Denmark before treatment. The variable - used widely was not language related (p<0.03). No difference was found for the sentence shimmer (% or/= irregularity).

No differences between the two examinations, with one month interval, were found for the controls with normal voices of sentence related jitter % and shimmer % or/= irregularity.

The results based on the clips of video stroboscopies were that the nodules were present in Croatia at both examinations, in Denmark 5 patients had a slight edema at the mid-membranous portion of the vocal cords at the second examination and the other 5 had remaining nodules.

Discussion

Objective values of the voices, before and after general medical treatment in a prospective case-control study, were achieved for 16 adult females with vocal cord nodules in a clinic in Copenhagen and a clinic in Zagreb during a summer period of two months.

The results of 16 patients with vocal nodules and voice complaints were compared with 24 adult females without vocal nodules and voice complaints. The study was based on a common prospective protocol for patients and controls. The inclusion criteria for the patients were digital stored pictures of vocal cord nodules, (primary outcome), reduced voice-related quality of life questionnaire (V-RQOL), acoustical measure of frequency and intensity of the voice jitter % and shimmer % (measured with MDVP), and a perceptive voice evaluation, of overall severity of voice pathology, roughness, breathiness and strain, (GRBAS test) (secondary outcome). Consent from the patients and traditional inclusion and exclusion parametres were used, but no males were found with vocal cord nodules in the period. An indication to a relation to the female sex role which till now has not been presented except in our Cochrane review where most of the patients were female(1).
In protocols for randomised prospective double blinded clinical trials of vocal nodules in the future (22), it is suggested that the medical (non-surgical, non-educational) aspects is an essential part (23). This is the reason why these kinds of evidence-based studies have to include large materials in the same way as in other medical fields (e.g. medical treatment of cancers) to obtain sufficient power of the studies.

The medical histories in this study indicate more infections in patients than in normal persons in the upper airways. A careful treatment of upper airway infections is therefore probably necessary for patients with vocal cord nodules, as based on this study, the double frequency in running speech, of course, playing a role of sensitivity to infections for females.

There is a measurable average improvement of the voices of the patients with vocal nodules with the GRBAS- voice perception test. This does correspond to average results of the MDVP.

In the V-RQOL questionnaire there is an overall better voice related quality of life for the social – psychological domain, less for the physical voice function domain. To learn to live (and sing) with a small voice handicap is part of the treatment, as it is the case for many very well-known pop-singers, but it is not ideal.

No differences were found between Croatians and Danes before and after a comparable medical treatment for vocal nodules for one month – at a whole, they were better. There is no evidence based studies related to the methods used, this is an expensive and time consuming trial to be carried out in the future understood by few outside the high quality research areas.

**Conclusion**

Upper airway disorders especially infections seem to be related to vocal cord nodules in women as found in the pilot study. No difference was found between Zagreb and Copenhagen. Allergy (mostly Immun Globulin E measurements) was not related. Other kinds of immunological deficiencies were also investigated in the study (e.g. non Immun Globulin E related allergies). An interesting aspect is that vocal cord nodules do not disappear by video stroboscopic examination.
even if the perceptive evaluation and the quality of life questionnaire, (V-RQOL) give a better voice function in both Zagreb and Copenhagen. Differences were found of the patients between Zagreb and Copenhagen: a partial disappearance of the vocal cord nodules was found in one half of the patients in Copenhagen but not in Zagreb.

As for the V-RQOL questionnaire, the physical voice functioning domain was worse in Copenhagen. The V-RQOL questionnaire of subjective voice complaints, and also the acoustical measurement with MDVP and the GRBAS perceptive evaluation test seem to be valuable in the ear-nose-throat clinics for clinical routine analysis of voice disorders, especially vocal nodules. As soon as possible, evidence based studies of the measurements should also be carried out.

<table>
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<th>Table 1. Patient discription</th>
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<td>Environmental provocations</td>
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<td>Others</td>
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</table>

GERD: Gastro-esophageal reflux disorder
LPRD: laryngeal-pharyngeal reflux disorder

Table 2. Voice-related quality of life questionnaire (V-RQOL), results of the prospective case-control pilot study of the new patients before medical treatment and after treatment, one month later, compared with normal controls (100% scores).
Table 3 The GRBAS voice perception test in patients and normal persons in Denmark and Croatia on a visual scale from 1-100 (1=best, 100=worst)
Table 4. The multidimensional voice program (MDVP) acoustical analysis: mean jitter% and shimmer% of /a/ and /i/ at the first and second examination with one month interval.
The first measurement (MDVP) and second measurement of all patients compared with controls in a case-control study. A reduction of shimmer% /i/ was found between the first and second examination (p<0.02). For shimmer% /a/ the same tendency was seen but not significant (p=0.053).

For description of sentence jitter%, see text.

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References
14. MDVP: Multidimensional Voice Program, Key-Elemetrics, Multispeech model 3700, ( see Appendix B for formulas from the Help section 5).


Appendix A (from ref.4)
Physical functioning:
I have trouble speaking loudly or being heard in noisy situations
I run out of air and need to take frequent breaths when talking
I sometimes do not know what will come out when I begin speaking

Psychological functioning:
I am sometimes anxious or frustrated (because of my voice)
I sometimes get depressed (because of my voice)

Social functioning:
I have trouble using the telephone (because of my voice)
I have trouble doing my work or practicing my profession (because of my voice)
I avoid going out socially (because of my voice)
I have to repeat myself to be understood
I have become less outgoing (because of my voice)

1 = none, not a problem
2 = A small amount
3 = A moderate (medium) amount
4 = A lot
5 = Problem is as “bad as it can be”
MDVP Key El.

Definition: Jitter Percent /% - Relative evaluation of the period-to-period (very short-term) variability of the pitch within the analyzed voice sample. Voice break areas are excluded.

Method: Jitt is computed from the extracted period-to-period pitch data (VOICE command) as:

\[
Jitt = \frac{1}{N-1} \sum_{i=1}^{N-1} \left| \frac{T_O^{(i)} - T_O^{(i+1)}}{N \sum_{i=1}^{N} T_O^{(i)}} \right|
\]

where: \( T_O^{(i)} \), \( i=1,2...N \) - extracted pitch period data,
\( N = \text{PER} \) - number of extracted pitch periods.

Definition: Shimmer Percent /% - Relative evaluation of the period-to-period (very short term) variability of the peak-to-peak amplitude within the analyzed voice sample. Voice break areas are excluded.

Method: Shim is computed from the extracted peak-to-peak amplitude data (VOICE command) as:

\[
Shim = \frac{1}{N-1} \sum_{i=1}^{N-1} \left| \frac{A^{(i)} - A^{(i+1)}}{N \sum_{i=1}^{N} A^{(i)}} \right|
\]

where: \( A^{(i)} \), \( i=1,2...N \) - extracted peak-to-peak amplitude data,
\( N \) - number of extracted impulses.

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22
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The patients in Zagreb were medically diagnosed and treated by BS, and controls stroboscoped by BS. N B-S made the tests and acoustic measurements in Zagreb.
The patients in Copenhagen were diagnosed and treated by MP, controls here were stroboscoped by MP, patients and controls were tested and acoustically measured by MP and computer assistant Christian Larsen.
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